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EXAMINER	
PANDE, SUCHIRA	
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1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,639	SCHWANEBERG, ULRICH	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/15/2009 and 11 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/15/2009 and 6/11/2009 has been entered.

Claim Status

2. Applicant has amended claim 1. Claims 1-15 are currently active and will be examined in this action.

Response to Arguments

Re 103 rejection of claims 1, 4-7, 12-13 and 15 over Henikoff in view of Zaccolo et al.

3. Applicant's arguments with respect to claims 1, 4-7, 12-13 and 15 have been considered but are moot in view of the new ground(s) of rejection. Applicant has amended base claim 1 to introduce limitation in step (iii)

--elongating the (+)-strands produced in step (ii) to the full length of the master sequence using the (-)-strand of the master sequence as a template strand for the elongation;---

Cited art does not teach this limitation hence rejection over previously cited art is no longer valid and is being withdrawn. New art is being cited that teaches all the elements of amended claim 1.

Re 103 rejection of claims 2, 8-11 and 14 over Henikoff and Zaccolo et al. as applied to claim 1 above further in view of Krokan et al. and Short et al.

4. Since rejection of claim 1 over Henikoff and Zaccolo et al. has been withdrawn. Hence rejection of claims 2, 8-11 and 14 over above references further in view of secondary references is no longer valid. Accordingly the rejections of claims 2, 8-11 and 14 over Henikoff ; Zaccolo et al. further in view of Krokan et al. and Short et al. are withdrawn.

Re 103 rejection of claim 3 over Henikoff; Zaccolo et al. ; Krokan et al. and Short et al. as applied to claim 2 above further in view of Lutz et al. and Cosstick & Vyle

5. Since rejection of claim 2 over Henikoff; Zaccolo et al. ; Krokan et al. and Short et al. as applied to claim 2 has been withdrawn. Hence rejection of claim 3 over above references further in view of secondary references Lutz et al. and Cosstick & Vyle is no longer valid. Accordingly the rejections of claim 3 over previously cited references is withdrawn.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 4-6, 12-13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koster et al. (US Pat. 6,428,955 B1 issued August 6, 2002 with priority back to November 6, 1996) in view of Brown et al. (US Pat. 6,239,159 B1).

Regarding claim 1, Koster et al. teach a process for the mutagenesis of a double-stranded polynucleotide sequence (master sequence) of n base-pairs having a (+)-strand and a complementary (-)-strand (see col. 35 line 29 where the CFTR gene is taught. Thus by teaching the CFTR gene Koster et al. teach a double-stranded polynucleotide sequence (master sequence) of n base-pairs having a (+)-strand and a complementary (-)-strand. Koster et al. further teach primers for PCR amplification of Exon 10 of CFTR gene. So for the purposes of the instant claim Examiner is restricting the master sequence to be limited to the region of CFTR gene comprising + and -strand amplified by the primers of SEQ ID NO 13 and SEQ ID NO 14) comprising the steps:

(i) creating a collection of single-stranded fragments of the (+)-strand of the master sequence wherein all members of the collection have the same 5'-terminus and have a deletion in the 3'-terminus such that the collection represents (+)-strands with a length of n-l, n-2, n-3,. .... nucleotides; (see col. 35 line 32 where PCR primer of SEQ ID NO 13 is taught to be biotinylated. See col. 35 line 33 where PCR primer of SEQ ID NO 14 is taught. The second primer is not biotinylated. When these primers are used for PCR amplification then amplified + strand of CFTR gene will have biotin label at its 5' end. While amplified –strand will have no biotin label. See col. 35 line 47 where affinity capture and denaturation of the double stranded DNA followed by washing (See col. 35 lines 59-60 where 3x washing is taught). Here PCR product of CFTR gene containing the biotin label at 5' end of + strand will allow binding of PCR product to streptavidin coated microtiter plate. Denaturation will lead to separation of the + and – strands. The biotinylated + strand will remain bound to streptavidin while denatured –strands lacking

biotin label will go into the wash bufffer. So the wash fraction will contain the amplified – strand. See col. 25 lines 35 where contacting target nucleic acid with specific exonuclease is taught. Also see col. 25 lines 54-55 where DNA sequencing by Mass Spectrometry via Exonuclease degradation is taught. Thus by teaching exonuclease degradation, Koster et al. teach use of 3' exonuclease. When + strands of above amplified DNA bound to microtiter plate at 5' end are target DNA then use of 3' exonuclease will result in creating a collection of single-stranded fragments of the (+) strand of the master sequence wherein all members of the collection have the same 5'-terminus and have a deletion in the 3'-terminus such that the collection represents (+) strands with a length of n-l, n-2, n-3,. .... nucleotides).

Regarding claim 1, step (ii) Koster et al. teach use of analogs (e.g. α-thio-modified nucleotides see col. 24 line 3) but do not teach introducing at least one universal or degenerate nucleotide at the 3'-terminus.

Regarding claim 1, Brown et al. teach

(ii) introducing at least one universal or degenerate nucleotide at the 3'-terminus of the (+)-strands produced in step (i) (see col. 2 lines 26-31 where universal or degenerate nucleotides are taught. Also see col. 19 example 11 lines 20-26 where introducing at least one universal or degenerate nucleotide at the 3'-terminus of the substrate by use of terminal deoxynucleotidyl transferase enzyme is taught. In the instant case the substrate is the (+)-strands produced in step (i). Thus this enzyme terminal deoxynucleotidyl transferase will act on the 3'-terminus of the (+)-strands produced in step (i) and add the universal or degenerate nucleotides analog to this end.

iii) elongating the (+)-strands produced in step (ii) to the full length of the master sequence using the (-)-strand of the master sequence as a template strand for the elongation (See Koster et al. col. 35 line 62 where annealing of primer to (+)-strands is taught. In the instant case the – strands that were present in the wash fraction are to be annealed to the (+)-strands produced in step (ii). This will result in a hybrid where 5' end of the (+) strand is immobilized by biotin tag via streptavidin to microplate. The 3' end of this biotin tagged (+) strand contains at least one universal or degenerate base. This (+) strand is annealed to (-) strand. The (+) strand is shorter than the (-) strand because it had been subjected to Exonuclease digestion. Hence in presence of extension conditions the 3' end of shorter (+) strand will be extended. See Koster et al. col. 36 line 2-4 where extension reaction in presence of dNTPs is taught. Thus teaching elongating the (+)-strands produced in step (ii) to the full length of the master sequence using the (-)-strand of the master sequence as a template strand for the elongation. This newly synthesized (+) (-) strand hybrid containing degenerate or universal bases in (+) strand will be bound to streptavidin plate); and

(iv) synthesizing a (-)-strand by using the (+)-strand produced in step (iii) as a template strand thereby effecting mutations in the (-)-strand at the positions of the previous universal or degenerate nucleotides compared to the master sequence. (see Koster et al. col. 35 line 57-58 where denaturation of Affinity captured double stranded DNA is taught followed by washing the wells. This denaturation will release the (-) strand while (+) strand produced in step (iii) will remain bound to the plate. Annealing primer of SEQ ID 14 to (+)-strand produced in step (iii) as a template strand followed by

Oligo base extension using dNTPs will result in synthesizing a (-)-strand by using the (+)-strand produced in step (iii) as a template strand thereby effecting mutations in the (-)-strand at the positions of the previous universal or degenerate nucleotides compared to the master sequence. See col. 35 line 62 where Oligo base extension is taught. Also see col. 36 line 2-4 where extension reaction in presence of dNTPs is taught).

Regarding claims 4 and 5, Brown et al. teach wherein step (ii) comprises the elongation of the collection of single stranded fragments produced in step (i) with universal base or degenerate base by enzymatic or chemical methods (see col. 19 example 11 lines 20-26 where use of terminal deoxynucleotidyl transferase enzyme is taught. Thus teaching step (ii) comprises the elongation of the collection of single stranded fragments produced in step (i) with universal base or degenerate base by enzymatic methods—claim 4 and wherein terminal deoxynucleotidyl transferase is used for elongation—claim 5).

Regarding claim 6, Brown et al. teach wherein deoxyinosine, 3-nitropyrrole, 5-nitroindole or a nucleotide analog with promiscuous base pairing property is used as a universal nucleotide in step (ii) (see col. 1 lines 28 and 29 where 3-nitropyrrole and 5-nitroindole are taught).

Regarding claim 12 Koster et al. teach wherein the elongation in step (iii) is effected by a PCR reaction (see col. 36 line 29 where PCR is taught).

Regarding claim 13 Koster et al. teach wherein step (iii) comprises the synthesis of a (-)-single stranded plasmid polynucleotide sequence from a double-stranded plasmid harboring the master sequence using a primer which anneals downstream of

the (+)-strand of the master sequence, and annealing of this (-)-single stranded-plasmid polynucleotide sequence with the (+)-strand produced in step (ii), and elongation of the (+)-strand (see col. 38 lines 9 where M13mp18 RF1 DNA is taught. M13 is single stranded phage. M13mp18 is a double stranded plasmid vector derived from M13 in which gene of interest is cloned in the polylinker region. The replicative form RF1 DNA refers to a double-stranded plasmid harboring the master sequence. See col. 37 lines 30-37 where primers for PCR are taught. As described in claim 1 above appropriate upstream and downstream primers are designed so as to be able to synthesise the desired region. Thus Koster et al. teach wherein step (iii) comprises the synthesis of a (-)-single stranded plasmid polynucleotide sequence from a double-stranded plasmid harboring the master sequence using a primer which anneals downstream of the (+)-strand of the master sequence, and annealing of this (-)-single stranded-plasmid polynucleotide sequence with the (+)-strand produced in step (ii), and elongation of the (+)-strand).

Regarding claim 15 Koster et al. teach wherein a PCR amplification is used after step (iii) in order to synthesize a (-)-strand complementary to the (+)-strand produced in step (iii), thereby effecting a double-stranded master sequence carrying mutations (see col. 35 line 29 where PCR amplification is taught).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Brown et al. in the method of Koster et al. The motivation to do so is provided by Brown et al. who state "The analogues are substrates for polymerase and terminal transferase enzymes" See

abstract. Further Brown et al. teach to one of ordinary skill in the art that degenerate analogues base pair with two or three natural bases, e.g. with pyrimidines (T/C) or Purines (A/G); while universal bases base pair with each of the natural bases without discrimination (see col. 2 lines 26-31). Hence one of ordinary skill knows from the teachings of Brown et al. that firstly these degenerate or universal nucleotides can be readily incorporated into DNA using DNA polymerase and or terminal transferase enzymes. Secondly once these degenerate or universal nucleotides are present in a location due to their ability to base pair with two or three natural bases or any of the 4 natural bases, during subsequent round of replication wherever such a degenerate or universal nucleotides has been incorporated in the (+) strand at the corresponding position mutations in the (-)-strand at the positions of the previous universal or degenerate nucleotides compared to the master sequence will be effected. Hence one of ordinary skill in the art has a reasonable expectation of success in being able to mutagenize all the positions of a double stranded DNA by practicing the method of Brown et al. in the method of Koster et al. at the time the invention was made without using toxic mutagenic chemicals. One of ordinary skill in the art recognizes that the resulting simple method is non toxic, hence does not require use of fume hoods or special handling required, which is necessary if one of ordinary skill is using the traditional DNA mutagens to perform mutagenesis of DNA. Another advantage of the method is that it can be performed easily by any ordinary artisan skilled in the art of performing PCR amplification.

8. Claims 2, 7-11 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koster et al. and Brown et al. as applied to claim 1 above further in view of Krokan et al. (US pat. 6,713,294 B1 with the national stage application 09/101,368 entry date of March 3, 1999 published first as WO97/25416 on July 17, 1997—previously cited) and Short et al. (US pat. 6238884 B1 filed March 9, 1999 previously cited) further in view of Zaccolo et al. (1996) J. Mol. Biol. 255: 589-603 (previously cited).

Regarding claim 2, Koster et al. and Brown et al. teach method of claim 1, but do not teach wherein the collection of single-stranded fragments in step (i) is created by incorporating nucleotide analogs and subsequent cleavage in alkaline or acidic solution.

Regarding claim 2, Krokan et al. teaches incorporation of uracil--a nucleotide analog into DNA (see col. 20 line 65). They teach release of uracil by use of Uracil DNA glycosylase from ss or ds DNA containing uracil (see col. 4 line 10). They also teach use of DNA glycosylase to generate an abasic site and subsequent cleavage (at pyridines) by alkaline solution or AP endonuclease. (see col 1 lines 21-44 and col. 18, lines 30-31). Thus Krokan et al. teach incorporating nucleotide analogs and subsequent cleavage in alkaline or acidic solution.

Regarding claim 8, Krokan et al. teaches use of a uracil containing primer to obtain uracil-containing DNA (see col. 16 line 64-67). This uracil-containing DNA is taught to be cleaved by Uracil DNA glycosylase (see col. 16 lines 60-62). By teaching a uracil containing DNA primer, Krokan et al. teach an oligonucleotide of the general formula

$p(U)_a(N)_b*(S)_c$[TERM]

with

p = 5'-phosphate or hydroxy-group or any chemical group capable of forming diester bonds (since the primer is taught to prepare uracil containing DNA therefore the primer must necessarily contain p = 5'-phosphate or hydroxy-group or any chemical group capable of forming diester bonds during the polymerization process, otherwise the primer could not be use to form the DNA)

U = universal or degenerate bases

a = arbitrary integral number from 0 to 10000. In this example of oligo taught by Krokan et al. a=0

N = mixture of four bases (A/T/G/C (standard nucleotides)) and b = arbitrary integral number from 0 to 100 (since primer is taught generally length of primers is between 10-50 nucleotide long. Thus by teaching a primer the oligo taught by Krokan et al meets the limitation of b= 0-100.

* -- cleavable group such as phosphothioate bonds in phosphothioate nucleotides. In the oligo taught by Krokan et al, no phosphothioate nucleotides are present hence the cleavable groups are necessarily absent.

S = standard nucleotide or nucleotide analog and c = arbitrary integral number from 0 to 100. In the example taught by Krokan et al. Uracil meets the limitation that S = standard nucleotide or nucleotide analog and c = arbitrary integral number from 0 to 100.

Regarding claim 8, Krokan et al do not specify the location where the uracil is incorporate in the primer. Since b is some number between 10-50 in the above situation and a=0 therefore oligonucleotide taught by Krokan et al. meets the proviso that a+b>0,

Krokan et al. teach use of [TERM] = a dye terminator or any group preventing elongation of the oligonucleotide, (see col. 27 line 35 where use of Dye terminator is taught. Here the sequencing is done by dye terminator cycle sequencing. Thus teaching that the dye terminator taught by Krokan et al. is [TERM] = a dye terminator or any group that prevents elongation of the oligonucleotide and hence causes termination).

Hence Krokan et al. teach use of Oligo to introduce universal or degenerate bases (taught by Zaccolo et al.) to the collection of single- stranded fragments created in step (i).

Regarding claim 9, Short et al. teach site directed mutagenesis, cassette mutagenesis (see col. 43 lines 49 and 50) Thus by teaching the two methods, Short et al teach wherein the oligonucleotide is designed in a way that

(a) stop codons and/or

(b) amino acids which disrupt secondary structures,

are avoided in the collection of the mutagenized polynucleotide sequences.

Regarding claim 7, Zaccolo et al. teaches wherein N4-hydroxy-2'-deoxycytidine (see page 597, par. 2), 8-oxodeoxy- guanosine triphosphate (8-oxo-G) (see abstract where 8-oxodGTP is taught) or a nucleotide analog with promiscuous base pairing property is used as degenerate nucleotide in step (ii).

Regarding claim 10, Zaccolo et al. teach wherein the oligonucleotide is designed in a way that

(a) transition mutations (Zaccolo et al. teach use of dPTP analog which yields transition mutations see abstract and several other base analog transition mutagens see page 590 par. 4)) or

(b) transversion mutations (Zaccolo et al. teach use of 8-oxodGTP which elicits transversions ---see page 591 par. 2),

are effected in the collection of the mutagenized polynucleotide sequences.

Thus by using the appropriate base analog taught by Zoccalo et al. as degenerate base in the oligo taught by Krokan et al. and Short et al. one would arrive at an oligonucleotide is designed in a way that (a) transition mutations or (b) transversion mutations are effected in the collection of the mutagenized polynucleotide sequences.

Regarding claim 11, Koster et al. teaches wherein the single-stranded fragment created in step (i) which is not ligated with the oligonucleotide is removed using exonuclease (see above for claim 1 where an exonuclease that degrades DNA starting from 3' end is taught).

When oligo that has 3' end blocked by terminator dye (taught by Krokan et al. is used) and it is ligated to the single stranded fragment created in step (i). Then all the molecules that have the oligo ligated to them will no longer have a free 3'OH group that can be attacked by Exo III. Thus this species of molecules will be resistant to Exonuclease digestion, where as the single-stranded fragment created in step (i) which

is not ligated with the oligonucleotide will still have a free 3'OH group hence it will be removed using exonuclease.

Thus by teaching 3' exonuclease, Koster et al. teaches wherein the single-stranded fragment created in step (i) which is not ligated with the oligonucleotide is removed using exonuclease.

Regarding claim 14, Zaccolo et al.; teaches wherein step (iii) comprises the synthesis of a (-)-single-stranded plasmid harboring the master sequence. They also teach use of appropriate primers. Thus Zaccolo et al. teaches a primer which anneals downstream of the (+)-strand of the master sequence and Zoccalo teaches elongation in the presence of analogs and degenerate nucleotides but does not recite use of uracil

Regarding claim 14, Krokan et al. teaches elongation in presence of uracil and standard nucleotides (see col. 20 example 2 where uracil containing DNA labeled with tritium is taught. By teaching this uracil containing DNA, Krokan et al. teach the elongation was in presence of uracil and standard nucleotides)

and after the elongation of the (+)-strand produced in step (ii), the uracil carrying (-)- single-stranded plasmid is digested with uracil glycosylase (see claim 2 above where use of uracil glycosylase is taught by Krokan et al. Thus in the instant case the (-) single-stranded plasmid will contain the uracil and this will be digested by uracil glycosylase.

It would have been prima facie obvious to one of ordinary skill in the art to use the method of Krokan et al. in the method of Koster et al. and Brown et al. at the time

the invention was made. The motivation to do so is provided by Zaccolo et al.; and Short et al.

Incorporation of degenerate nucleotides, (as taught by Zaccolo et al.), during elongation results in random mutagenesis over the entire region being elongated.

However if one was interested in mutating a specific enzymatic domain of an enzyme while ensuring that other parts of the enzyme were unchanged. Then if one were to use the oligos that had the degenerate nucleotides/etc predesigned in the oligonucleotide then one could make targeted mutants by designing the oligos targeted for specific parts of the sequence to be changed. This is corroborated by a patent issued to Short et al. that teaches directed evolution by performing site saturated mutagenesis where oligos are used to direct mutation of the desired amino acids. (See Short et al. section labeled Saturation Mutagenesis col. 34 lines 54-67 where use of proprietary codon primers (oligos) is taught to introduce point mutations).

Zaccolo et al. teach use of degenerate nucleotides that are potent mutagens with known mode of action. Thus by using appropriate degenerate nucleotides in the specific location of the oligonucleotide, one can design oligos that will generate transitions or transversions in those specific locations.

In view of the above teaching one of ordinary skill can design oligos that would be targeted to the specific part of the sequence to be mutated.

9. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Koster et al. ; Brown et al. ; Krokan et al. ; Short et al. and Zaccolo et al. as applied to claim 2 above further in view of Lutz et al. (2001) Nucl. Acids Res. Vol. 29 No 4 e 16-previously

cited; and further in view of Cosstick & Vyle (1990) Nucleic acids Res. Vol. 18 No 4 pp 829-835-previously cited.)

Regarding claim 3, Koster et al. ; Brown et al. ; Krokan et al. ; Short et al. and Zaccolo et al. teach method of claim 2, but they do note teach wherein the nucleotide analog is an alpha-phosphothioate nucleotide and oxidative cleavage is achieved by iodine at the phosphothioate bonds.

Regarding claim 3, Lutz et al. teach wherein the nucleotide analog is an alpha-phosphothioate nucleotide (page 3 of 7 where DNA spiking by PCR in presence of alpha-phosphothioate nucleotide is taught). Lutz et al. teach use of Exo III for cleavage of DNA. But they do not teach cleavage by iodine at the phosphothioate bonds.

Regarding claim 3, Cosstick & Vyle teach oxidative cleavage is achieved by iodine at the phosphothioate bonds (see abstract where they state the P-S bond is readily cleaved by solution of iodine).

It would have been prima facie obvious to one of ordinary skill in the art to practice the method of Lutz et al in the method of Koster et al. ; Brown et al. ; Krokan et al. ; Short et al. and Zaccolo et al. at the time the invention was made. The motivation to do so is provided by Cosstick & Vyle.

Cosstick & Vyle state "oligonucleotides containing phosphorothioate linkages have proved useful tools for the study of DNA processing enzymes and DNA structure. In addition their increased resistance to nuclease activity suggests a potential application in the antisense approach to viral chemotherapy" (see page 829 par. 1 introduction). They go on to state "Procedures have been developed which enable ----to

be incorporated into dinucleotide phosphate analogues using phosphoramidite chemistry. The synthetic methods are compatible with automated, solid phase synthesis of oligodeoxynucleotides -----. The ease with which the modified linkage is cleaved in the presence of silver ions or iodine solutions suggests that the incorporation if 3'-S-phosphorothioate linkages into oligonucleotide primers and their subsequent chemical cleavage may prove a useful technique for the 'nicking' and manipulation of DNA.

Conclusion

10. All claims 1-15 under consideration are rejected over prior art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Suchira Pande/
Examiner, Art Unit 1637